I HEARBY CERTIFY THAT THIS IS BEING DEPOSITED WITH THE UNITED STATES PATENT AND TRADEMARK OFFICE VIA THE ELECTRONIC FILNG SYSTEM (EFS) ON:

September 14, 2011

/Janet A. Sherrill/ September 14, 2011
SIGNATURE DATE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Jean F. Welter et al.
Serial No.	:	10/578,212
Filing Date	:	May 4, 2006
For	:	APPARATUS AND METHOD FOR TISSUE ENGINEERING
Group Art Unit	:	1797
Confirmation No.	:	7563
Examiner	:	Nathan Andrew Bowers
Attorney Docket No.	:	CWR-6622US PCT

Mail Stop Appeals – Reply Brief
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REPLY BRIEF

Sir:

This Reply Brief is in response to the Examiner's Answer dated July 14, 2011. This Reply Brief addresses the grounds of rejection set forth in section (9) of the Examiner's Answer and the response to arguments in section (10) of the Examiner's Answer.

Claim 1

Rejections under 35 U.S.C. §102

Claim 1 recites that a hydrostatic loading module transmits hydrostatic pressure through a membrane to a first liquid medium contained in a first chamber. The Appellant maintains that the hydrostatic pressure is positively recited and, thus, the bioreactor of Vetillard must actually transmit – not just be capable of transmitting – hydrostatic pressure. Nonetheless, the Examiner asserts that Vetillard is inherently capable of imparting a hydrostatic pressure on the zone C2 by sealing the zones C1, C3 surrounding the cell culture chamber by controlling when fluid is added and withdrawn (Examiner's answer page 13). There is no indication, however, that either zone C1 or C3 in Vetillard are sealed. In fact, there are no valves, orifices, or other structure in Vetillard to seal the moving liquid media F1 within the zone C1 and while there is a valve V3 downstream of the zone C3 there is no structure at the input side of the zone C3 that can statically seal the liquid media F3 within the zone C3.

Nonetheless, the Examiner asserts that the zone C1 could be filled with the media F1 and the pump P1 turned off such that fluid within the zone C1 and below the inlet tube EF1 and outlet tube SF1 remains static and thereby imparts hydrostatic pressure upon the membrane M1 (Examiner's Answer page 13). The bioreactor of Vetillard is not capable of operating in this manner because the bioreactor of Vetillard would not properly function if the liquid media F1 and F3 were not actively flowing through the respective zones C1 and C3. In particular, for the reasons previously discussed, the bioreactor is specifically designed to operate under

hydrodynamic – not hydrostatic – conditions. Accordingly, operating the bioreactor of Vetillard under hydrostatic pressure as the Examiner asserts would significantly reduce the efficacy and efficiency of both the "downward phase" and "ascending phase", thereby deleteriously affecting the culture cells within the zone C2. A continuous, fresh supply of the liquid media F1, F3 maintains a constant diffusion of desired proteins, etc., through the membrane M1, M3 during the respective phase cycle. For these reasons, the bioreactor of Vetillard is not capable of operating under hydrostatic conditions as the Examiner asserts.

Furthermore, the Examiner contends that nowhere in the Appellant's written description, Figures or claims are valves or other sealing means used to trap fluid within the first and second loading modules, *i.e.*, provide hydrostatic pressure, ever described or depicted (Examiner's Answer page 14). Accordingly, the Examiner asserts that since there are no structural differences between the claimed invention and that of Vetillard, Vetillard must be capable of fulfilling the intended use, *i.e.,* hydrostatic loading, recited in claim 1.

The specification of the present invention states that:

> Referring to FIG. 7, the first member 120 can also include a pressure sensor 158 (e.g., SenSym-ICT) that monitors the pressure in the first outer chamber 104. *The pressure sensor [158] can be connected to a computer (not shown) that modulates the output flow and pressure of pumps (not shown) that supply the second liquid medium 110 to the first outer chamber 104 and the second outer chamber 106*.
>
> During operation of the bioreactor system 10, the first liquid medium 31 can be readily perfused through the bioreactor chamber 30 using a pump (not shown) and the second liquid medium 110 can be readily perfused through first outer chamber 104 and the second outer chamber 106. When pressurizing the bioreactor chamber 30, the inlet port 50 and the outlet port 52 are closed using medium control valves

> 60 and 62. The hydrostatic pressure in the first and the second outer chambers 104 and 106 is increased and hydrostatic pressure is applied across the gas permeable membranes 22 and 24 to the bioreactor chamber 30. *Pressure in the chamber 30 is monitored by the pressure sensor 158 and modulated by controlling pump speed and a flow outlet restrictor (not shown) with a computer. This design allows the application of arbitrary hydrostatic pressure waveforms and physiologically relevant hydrostatic loading of cells or tissue 15 cultured, grown, or incubated in the bioreactor chamber 30 without removing the specimen or otherwise breaching the bioreactor system 10.*
>
> By way of example, the loading regimen can be 1 hour on, 1 hour off, 24 hours a day, 7 days a week for 21 days. During the "on" hour, hydrostatic load can be applied following a pre-programmed sinusoidal waveform between 0 and 1000 kPa.

(Page 1, lines 7-12, Page 16, lines 14-27, and Page 20, lines 19-24; Figs. 2 and 7). It is therefore clear that the hydrostatic loading module of the present invention uses specific structure, *e.g.,* a computer, pressure sensor 158, and a flow outlet restrictor, to control the output flow and pressure of the pumps supplying the second liquid medium 110 to the first outer chamber 104 and the second outer chamber 106 to apply sinusoidal hydrostatic pressure waveforms to the chamber 30.

Since there is no indication that Vetillard includes identical or similar structure to that used in the present invention to apply hydrostatic pressure to the chamber 30, it cannot be said that Vetillard is capable of applying hydrostatic pressure to the bioreactor zone C2 as the Examiner asserts. Based on the foregoing, it is respectfully submitted that claim 1 is not anticipated by Vetillard and is therefore allowable.

Rejections under 35 U.S.C. §103

In the alternative, the Examiner asserts that one having ordinary skill in the art would operate the bioreactor of Vetillard under hydrostatic conditions based on the

teachings of Jensen. The only references to hydrostatic loading in Jensen, however, are generalizations about operating parameters of the microfermentor (Paragraphs 190 and 194). Jensen does not give any specifics whatsoever regarding structure or other means to apply and/or adjust hydrostatic pressure within the microfermentor. One having ordinary skill in the art, having read the generalized teachings of Jensen related to hydrostatic pressure could not then modify the bioreactor of Vetillard to operate under hydrostatic pressure because Jensen provides no guidance, specifics or teachings sufficient to enable one having ordinary skill in the art to modify the bioreactor of Vetillard as the Examiner asserts.

Regardless, as noted, one having ordinary skill, seeking to modify the bi-directional, alternating dynamic fluid media bioreactor of Vetillard, would not look to the single direction, single fluid media bioreactor of Jensen. Accordingly, one having ordinary skill would not modify Vetillard to operate under hydrostatic pressure as taught in Jensen.

The Examiner asserts that Jensen makes it clear that hydrostatic loading is a well known, functionally equivalent substitute for nutrient perfusion via dynamic, bidirectional flow because Jensen teaches that hydrostatic pressure may be used to predictably and successfully delivery key gases and metabolites across a membrane (Examiner's Answer page 17). To the contrary, Jensen teaches that hydrostatic pressure may be present on one side of a membrane during single-direction fluid flow in a microfermentor. There is no indication that hydrostatic loading would function equivalently in a bioreactor where bi-directional flow is maintained on opposing sides of two membranes. More specifically, there is no indication that

hydrostatic loading would allow for the same downward migration of growth hormones, large proteins, and wastes in the "downward phase" and the same upward migration of growth hormones croissance, large proteins, and wastes in the "upward phase" as taught by Vetillard because hydrostatic pressure is only present in Jensen in the upward migration of water, carbon dioxide, and oxygen and simultaneous downward migration of oxygen, nutrients, and products. Accordingly, it cannot be said that the alleged substitution of hydrostatic loading for the hydrodynamic loading of Vetillard yields the predictable result of producing the same or functionally equivalent bi-directional flow through two membranes in Vetillard as the Examiner asserts.

Claim 43

Claim 43 recites that the inlet port and the outlet port are sealed during hydrostatic loading to allow the hydrostatic pressure of the first chamber to be increased without loss of first liquid medium from the first chamber.

The Examiner asserts that the valves V2E1-V2E3 may be closed to seal the input side of the zone C2 and the valves V2S1-V2S3 may be closed to seal the output side of the zone C2 (Examiner's Answer page 15). Claim 43, however, does not recite that the inlet and outlet ports *can* be sealed but rather positively recites that the inlet and outlet ports *are* sealed. Vetillard does not teach that all three valves V2E1-V2E3 are closed at the same time or that all three valves V2S1-V2S3 are closed at the same time. Rather, Vetillard states that one of the valves V2E1-V2E3 is always open depending on the process being performed, *e.g.,* inoculation, gene transfer or rinsing, and that one of the valves V2S1-V2S3 is always open

depending on the output path of the fluid from the zone C2, *e.g.,* a recovery tank, a tank R2 or a waste disposal tank (*see* Paragraphs 147-148 and 151-154; Fig. 6).

At no point in the operation of the bioreactor of Vetillard are all the valves V2E1-V2E3 and V2S1-V2S3 closed. Regardless, since the valves V2E1-V2E3 are spaced from the zone C2 on the opposite side of the pump P2 closing all the valves V2E1-V2E3 will not statically retain the liquid media F2 exclusively within the zone C2. Accordingly, the zone C2 would not be sealed as the Examiner asserts. Based on the foregoing, it is respectfully submitted that claim 43 is not anticipated by Vetillard and is therefore allowable.

Claim 44

Claim 44 recites that the second chamber is sealed to pressurize the second the second liquid medium and thereby transmit hydrostatic pressure through the gas permeable membrane and into the first chamber.

The Examiner asserts that both of Vetillard's zones C1 and C3 are sealed to the membranes M1 and M2 of the cell culture chamber or zone C2 to prevent external contamination and leakage from the bioreactor and allowing for the transmission of hydrostatic pressure (Examiner's Answer page 15). It is clear from Fig. 6 of Vetillard, however, that there is no structure to seal the zone C1 as the fluid media F1 freely and continuously flows from the pump P1, through the C1, and into the tank R1. Regarding zone C3, at no point are all of the valves V2E1-V2E3 and V2S1-V2S3 closed to seal the zone C3 and, regardless, the valves are all spaced from the zone C3 and therefore cannot seal the zone C3 as liquid media F3 trapped between the valves would still be capable of flowing into and out of the zone. Based

on the foregoing, it is respectfully submitted that claim 43 is not anticipated by Vetillard and is therefore allowable.

In view of the foregoing, Appellants respectfully submit that the rejections of claims 1-14 and 42-44 are improper and should be reversed. Reversal of the rejections of claims 1-14 and 42-44 is respectfully requested.

Please charge any deficiency or credit any overpayment in the fees for this Reply Brief to our Deposit Account No. 20-0090.

Respectfully submitted,

/Richard A. Sutkus/
Richard A. Sutkus
Reg. No. 43,941

TAROLLI, SUNDHEIM, COVELL,
& TUMMINO L.L.P.
1300 East Ninth Street, Suite 1700
Cleveland, Ohio 44114
Phone:(216) 621-2234
Fax: (216) 621-4072
Customer No.: 68,705